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KUNZ, G	
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DATE MAILED: 11/10/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 7-11-94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 9-10 AND 15-16 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-8 AND 11-14 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 9-10 AND 15-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Applicant's Amendment B and Information Disclosure Statement filed July 1, 1994 (Papers Nos. 9 and 10) have been received and entered into the record.

Claims 9 - 10 and 15 - 16 are pending in the case.

Applicant's submission of a substitute Abstract is acknowledged.

> 35 U.S.C. § 101 reads as follows:
> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Any 35 USC statutes not cited in the Office action may be found cited in full in the first Office action (Paper No. 4) mailed July 1, 1993.

Claims 9 - 10 and 15 - 16 are rejected under 35 U.S.C. § 101 because the invention lacks patentable utility.

The claims are drawn to oligonucleotide possessing a 2'-O-modification. The utility of such a compound is set forth on page 20, second paragraph:

> The oligonucleotides of the present invention can used in diagnostics, therapeutics, and as research reagents. For therapeutic use, an animal having a disease characterized by the undesired production of a protein is contacted with an oligonucleotide of the present invention having a sequence of nucleotide bases specifically hybridizable with a selected sequence of RNA or DNA coding for said protein.

Whether the use of the claim modified oligonucleotides is as simply hybridization probes or as antisense therapeutics, the utility of said compounds rests upon their specific hybridization

potential. Claims 15 - 16, the narrowest claims, are directed to the 2'-O- modification being either a C4 to C20 or a C5 to C20 alkyl moiety possessing one or more of numerous substituents. The largest alkyl moiety which applicant reports preparing is the 5'-O-pentyl nucleoside (page 24, Example 7). However, there is no data documenting the efficacy of oligonucleotides with one or all nucleotides modified with pentyl at the 5'-O-position. Furthermore, Iribarren et al. (PNAS 87: 7747 - 7751, 1990) specifically states that such 5-carbon modifications of the 2'-O-positions inhibits the binding of said oligonucleotide to complementary RNA. In view of Iribarren et al.'s teaching combined with the disclosure's failure to document the hybridization binding of a representative number of oligomers having 2'-O-alkyl groups covering the range of C4 to C20, the examiner has good and sufficient reason to believe that the person of ordinary skill in the art at the time of the invention would not believe that bulk and long chain modifications of the 2'-O-positions of nucleotides in oligomers would be able to hybridize with sufficient strength to their complementary polynucleotide.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first

paragraph, as failing to provide an adequate written description and failing to teach adequately how to use the invention, i.e. failing to provide an enabling disclosure.

As detailed above in the lack of utility rejection, the Iribarren et al. reference documents that the prior art would not have accepted stated utility of the claimed 2'-O-modified oligonucleotides without clear and convincing evidence. The disclosure fails to provide such documentation. While the specification does teach one how to prepare nucleotides with 2'-O-imidazoyl, 2'-O-pentyl, 2'-O-nonyl, 2'-O-N-phthalimido groups, there is no data documenting the hybridization binding of oligonucleotides having some or all nucleotides so modified. Thus the person of ordinary skill in the art at the time of the invention would not have been able to use the claimed oligonucleotides as even hybridization probes when the 2'-O-positions of the oligomer were modified with large (greater than five carbon atoms) bulky (secondary and tertiary carbon isomers) alkyl groups. An invention that lacks utility is also by definition not enabled.

Claims 9 - 10 and 15 - 16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 9 - 10 are rejected under 35 U.S.C. § 103 as being unpatentable over Cotten et al. (Nucl. Acids Res. 19: 2629, 1990).

Claims 9 - 10 are directed to 2'-O-derivatives of guanosine and 2-amino-adenosine which can be incorporated into oligonucleotides. Each claim encompasses 2'-O-ethyl modifications with at least one halogen such as fluorine.

Cotten et al. discloses 2'-O-ethyl containing oligoribonucleotides possessing increased binding affinity for complementary polynucleotides (page 263, first paragraph under Discussion, lines 4 - 7). The substitution of a fluorine atom for a hydrogen atom in the 2'-O-ethyl group would not change the effective size of said group. Consequently, the person of ordinary skill in the art at the time of the invention would have expected that a fluoroethyl group would possess the same hybridization properties as the 2'-O-ethyl modified oligomers.

While Cotten et al. does not discloses 2'-O-ethyl derivatives of 2-aminoadenosine, the examiner takes Official notice that the prior art recognizes that the substitution of 2'-aminoadenosine for adenosine in an oligonucleotides enhances the hybridization affinity. Consequently, the person or ordinary skill in the art with the Cotten et al. reference before him would have found the claimed 2'-O-modified guanosine and 2-aminoadenosine derivatives to have been obvious for the purpose of synthesizing an oligonucleotide with enhanced binding affinity. Thus, the invention is <u>prima facie</u> obvious in the absence of clear and convincing evidence to the contrary.

The applicant argues against this rejection on the grounds

that Cotten et al. does not discloses 2'-aminoadenosine. This argument has been fully considered but is not deemed persuasive. The examiner has taken Official Notice that 2-aminoadenosine is well known in the art at the time of invention and that this nucleoside is known, when substituted for adenosine, yields an oligonucleotide with enhanced hybridization affinity.

The applicant further argues against this obviousness rejection on the grounds that the artisan would have had difficulty in synthesizing the claimed compounds, particularly the guanosine derivatives, as noted by Keller et al. because of the need to use very reactive electrophiles (p. 884, paragraph 2). This argument has been fully considered but is not deemed persuasive. While efficient synthesis of 2'-O-guanosine derivatives may be been difficult at the time of the invention, the level of skill in the art of organic chemistry is quite high. Therefore, the person of ordinary skill in the art would certainly have recognized the necessity of using strong electrophiles to alkylate guanosine. However, this obviousness rejection does not depend upon the artisan achieving a highly efficient synthesis of 2'-O-modified guanosine, but only that he achieve some synthesis!

Claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Iribarren et al. in view of Wagner et al. (Nucl. Acids Res. 19: 5965 - 5971, 1991).

Claim 15 is directed to 2′-O-modified guanosine derivatives, wherein the 2′-O- group may be an alkyl group having from four to twenty carbon atoms.

Iribarren et al. discloses 2′-O-ethyl oligonucleotides and that they possess increased binding affinity for polynucleotides and are resistant to nuclease digestion. This reference further guides the artisan to four-carbon alkyl 2′-O-modifications on page 7750, column 2, last paragraph, lines 1 - 6)

Iribarren et al. does not specifically discloses 2′-O-modified guanosine. However, the person of ordinary skill in the art would have expected that any and all nucleotides in an oligonucleotides would yield enhance hybridization binding with a 2′-O-ethyl modification.

However, Wagner et al. does disclose 2′-O-ethyl guanosine (page 5966, Figure 2) and 3′-O-phosphoramidite derivatives.

Consequently, the 2′-O-n-butyl guanosine derivatives would have been obvious to the person or ordinary skill in the art at the time of the invention wanting to develop yet other 2′-O-modified oligonucleotides possessing comparable hybridization affinity to those having a 2′-O-ethyl modification. Thus, the invention is <u>prima facie</u> obvious in the absence of clear and convincing evidence to the contrary.

The applicant argues against this rejection on the

ground that Iribarren et al. does not disclose 2'-O-modified guanosine derivatives. This argument has been fully considered but is not deemed persuasive. The new Wagner et al. reference does bridge this deficiency of Iribarren et al. Again, the artisan would not have been required to possess a highly efficient synthesis of 2'-O-butylguanosine in order for this obviousness rejection to be proper. The artisan would only have needed to be able to synthesis a workable amount even with an inefficient synthesis.

Claim 16 is rejected under 35 U.S.C. § 103 as being unpatentable over Iribarren et al. in view of Wagner et al. for the reasons given presented above for the rejection of claim 15. The only substantive difference between the two claims is the minimum number of carbon atom cut off. The minimum cut off for claim 15 is **four carbon atoms.** For claim 16 the minimum cut off is **five carbon atoms.** The applicant argues against this rejection on the ground that Iribarren et al. teaches against five carbon atom alkyl groups at the 2'-O-position on page 7750, column 2, last paragraph. This argument has been fully considered but is not deemed persuasive. A discriminating reader of the Iribarren et al. article would have noticed that the five carbon alkyl group tested by Iribarren et al. was not the straight chain compound but the bulkier branched 3,3-dimethyl allyl group (page 7750, column 2, lines 5 - 8.

The artisan would have not concluded from this data that all five carbon atom alkyl groups would not have worked, but that bulky branched alkyl groups would not have functioned to increase the hybridization affinity.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Robinson, can be reached on (703) 308-2897. The fax phone number for this Group is (703) 305-3230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Gary L. Kunz, Ph.D.
October 30, 1994